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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,122	02/06/2004	Thomas P. Zwaka	960296.99021	8384

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Nicholas J. Seay
Quarles & Brady LLP
P O Box 2113
Madison, WI 53701-2113

EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
10/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,122	ZWAKA ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-18* is/are pending in the application.

4a) Of the above claim(s) *5,6,11 and 14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7-10,12, 13, 17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/30/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 3-18 are pending in the instant action. Claims 5, 6, 11 and 14-16 are withdrawn. Therefore, claims 1, 3, 4, 7-10, 17 and 18 are under examination in this action.

This application contains claims drawn to an invention nonelected with traverse in the response filed 7/30/07. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 112, second paragraph on pages 6 and the claim rejections under 35 U.S.C. 112, first paragraph on pages 6-7 of the amendment filed 7/30/07. Applicants' arguments filed 7/30/07 have been fully considered and are persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 4, 7-10, 12, 13, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Benvenisty et al (US 2002/0127715 or WO 02/061033); see entire documents) in view of West et al (US 2004/0219563; see entire document). **This rejection is maintained for reasons of record in the office action mailed 3/12/07 and restated below.**

Applicants claims are drawn to modification of hES cells by electroporation of a genetic construct comprising a foreign gene and homologous regions for recombination into the hES genome followed by identification of cells comprising the genetic construct and purification of the cells in which the marker is a marker of cell lineage of differentiation. Furthermore, gene expression profiled from the purified cells is analyzed.

Benvenisty et al teach electroporation of genetic constructs into human embryonic stem cells to transform cells with a construction comprising a marker for identification and purification of transformed cells(see e.g. ¶ 0008- ¶0009, 0044 and 0062). The construct comprises a fluorescence marker or any other type of marker protein that is used to distinguish transformed cells from those absent such sequences such as for example by FACS analysis (see e.g. ¶ 0008, ¶ 0010 and ¶0012). The marker comprises a promoter that is specifically active in cells in a desired state i.e. undifferentiated (see e.g. ¶ 0012 and 0047) or differentiated states leading to different lineages (see e.g. ¶ 0054).

Benvenisty et al do not teach that the vector is integrated by homologous recombination or that the marker is inserted into regulatory regions of the genome such that its expression is regulated according to its state of differentiation.

In ¶0180, West et al state that DNA markers can be inserted into human genes by homologous recombination. The markers are either inserted into sites so that they are transcriptionally regulated by the promoters of the genes into which they are inserted (see e.g. ¶0131) or comprise exogenous promoters that are development stage specific promoter/regulatory elements (see ¶0199). In these methods it is preferable to use homologous recombination for insertion of the construct comprising a marker into a specifically selected site

in a gene that is conditionally expressed in a differentiating cell to disrupt and inhibit expression of the endogenous gene to produce a knockout or inserted to be transcribed ¶0073. The method of West et al allows for isolation of cells in distinct differentiated states such that the gene profile can be determined (see e.g. ¶0199).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to methods of random insertion taught by Benvenisty with the methods of homologous recombination such as insertion of a promoterless marker into the genome in a sight that is regulated by the stage of differentiation as taught by West et al because Benvenisty et al teach that it is within the ordinary skill of the art to transform a hES by electroporation with markers to identify transformed and differentiated cells and because West et al teach that it is within the ordinary skill of the art to use homologous recombination with these cells for directed stable integration such as in specific regions or genes that are stage or lineage specific. One would have been motivated to do so in order to receive the expected benefit of insertion of the construct comprising a marker into a specifically selected site such that cells of specific lineage can be isolated and the genetic profiles of the cells determined. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 103 on pages 7-11 of the amendment filed 7/30/07. Applicants' arguments filed 7/30/07 have been fully considered but they are not persuasive. Benvenisty et al demonstrate that the ability to transform mammalian

cells and specifically human ES cells by electroporation was known in the art at the time of filing. ¶ 0010 specifically states "In another embodiment of the invention, a method is provided for altering gene expression in a population of human embryonic stem cells; that includes introducing into the population of cells by electroporation or in the presence of a cationic polymer." That Benvenisty cites within the specification patents that teach manipulating mouse stem cells does not affect the teachings clearly set forth in Benvenisty et al that human ES cells can be transformed by electroporation. In fact, applicants demonstrate that this method is more successful then transfection by lipofectamine and as successful as fugene (see figure 1). Applicants provide an article from Milwaukee Journal Sentinel and one from Genomics and Genetics Weekly that states that applicants have developed the means of swapping genes in human ES cells. However, the article suggests that the novelty of the invention is that inventors are able to electroporate hES cells "Scientists manipulate genes through electroporation - giving an electric shock to a cell, which makes small holes in its membrane so new DNA can be taken in. While mice and people are similar in many ways, it turned out they're quite different in this respect. In mice, the technique can be done on single cells, but human cells are more social and need to b e electroporated in clumps or near each other for it to work, Zwaka said. He and Thomson also had to modify the voltage they used and other factors to get it to work on human cells".

However, Benvenisty et al also teach that hES cells can be electroporated. What is missing from Benvenisty et al is teachings that the construct can be targeted to specific sites within the genome. However, the art recognizes that this method was well known at the time of filing. For example, West et al teach that "Alternatively, gene trapped stem cells useful for these

methods can be made by inserting marker DNA constructs into targeted sites in the conditionally expressed gene by known methods utilizing homologous recombination" ¶ 0131. Applicants argue that West et al does not predate the instant invention. However, West et al is a non-provisional application that claims priority to a provisional application filed 10/16/2002 and therefore does predate the instant case, which has a filing date of 2/7/03. As well, while applicants indicate that Benvenisty and West et al encompass other teachings then electroporation, use of human cells and targeted insertion, the teachings of each of these references must be considered as whole. Specific teachings that demonstrate that relevant embodiments related to electroporation, use of human cells and targeted insertion were taught and/or demonstrated have been presented above.

Conclusion

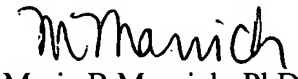
THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Maria B Marvich, PhD
Examiner
Art Unit 1633